Synopsis of the thesis

Synthesis, Characterization & Pharmacological Evaluation of New Coumarin Derivatives And Development of New Synthetic Methodologies Besides Investigations of Capped Silver & Gold Nanoparticles for Electrical Impedance Properties

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In Chemistry

Submitted by

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SYNOPSIS

The thesis entitled "**Synthesis, Characterization & Pharmacological Evaluation of New Coumarin Derivatives besides Development of New Synthetic Methodologies and Investigations of Capped Silver & Gold Nanoparticles for Electrical Impedance Properties**" is divided into five chapters which are again subdivided into two sections.

CHAPTER-I: **Synthetic approaches and biological applications of coumarins: A review.**

In this Chapter introduction, previous synthetic approaches and different biological applications exhibited by coumarins was thoroughly discussed.

CHAPTER-II: **Design, synthesis, x-ray characterization of some new 2-(4-methy-2-oxo-2*H*-chromen-7-yloxy) acetamide derivatives and their anti-proliferative & anti-asthmatic studies**

Section-A: This section describes introduction and previous synthetic approaches of carboxamide derivatives of coumarins.

Section-B: This section consists of present work including the synthesis of substituted 2-(4-methy-2-oxo-2H-chromen-7-yloxy) acetamides and their characterization and Single crystal XRD studies were discussed.

Section-C: In this section, different biological applications of synthesized coumarin derivatives were examined.

CHAPTER-III: **An efficient and cost-effective microwave-assisted affable reaction for aminolysis of epoxides on reusable solid media: Application in the synthesis of (RS)-Propranolol (A Cardiovascular Drug)**

Section-A: This section describes introduction and previous synthetic approaches of β-amino alcohol compounds in organic synthesis.

Section-B: This section consists of present work including the synthesis of β-amino alcohol compounds promoted by silicaperchloric acid catalyst under solvent-free conditions & their spectral characterization.

CHAPTER-IV: **Nano Copper ferrite: A reusable catalyst for the synthesis of β, γ-Unsaturated Ketones**

Section-A: This section describes introduction and previous synthetic approaches of β- γ-Unsaturated Ketones in organic synthesis.

Section-B: This section consists of present work including the synthesis of Copper ferrite nanoparticle and β- γ-Unsaturated Ketones promoted by Copper ferrite nanoparticle catalyst under solvent-free conditions & their spectral characterization.

CHAPTER-V: **Facile synthesis & Characterization of thiosemicarbazide capped Silver & Gold nanoparticles and study of their impedance measurement.**

Section-A: This section describes introduction to previous methods of synthesis & applications of silver & gold nanoparticles.

Section-B: This section consists of present work including the Synthesis of thiosemicarbazide capped silver & gold nanoparticles via chemical reduction method & Study of their electrical impedance property at room temperature.

CHAPTER-I:

Interest in coumarin chemistry has flourished for many years; basically from a result of the wide spread use of coumarin derivatives. Coumarin was basic molecule found in family of many derivatives, like a simplest naturally occurring phenolic substance possessing fused benzene and α-pyrone rings

Coumarins comprise a group of natural compounds, found in a variety of plant sources. The very long association of plant coumarins with various animal species and other organisms throughout evolution may account for the extraordinary range of biochemical and pharmacological activities of these chemicals in mammalian and other biological systems. Coumarins have important effects in plant biochemistry and physiology, acting as antioxidants, enzyme inhibitors and precursors of toxic substances. In addition, these compounds are involved in the action of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection. The coumarins have long been recognized to possess anti-inflammatory, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticancer activities. In addition, coumarins are known to be lipid lowering agents with moderate triglyceride lowering activity. Furthermore, hydroxycoumarins are powerful chain-breaking antioxidants and can prevent free radical injury by scavenging reactive oxygen species.

Over and above, the discoveries made by isolation of coumarins from the hundreds of species of plants and other organisms, and the derivatives of synthetic origin significantly increases the number of coumarin structures known till date.

CHAPTER-II:

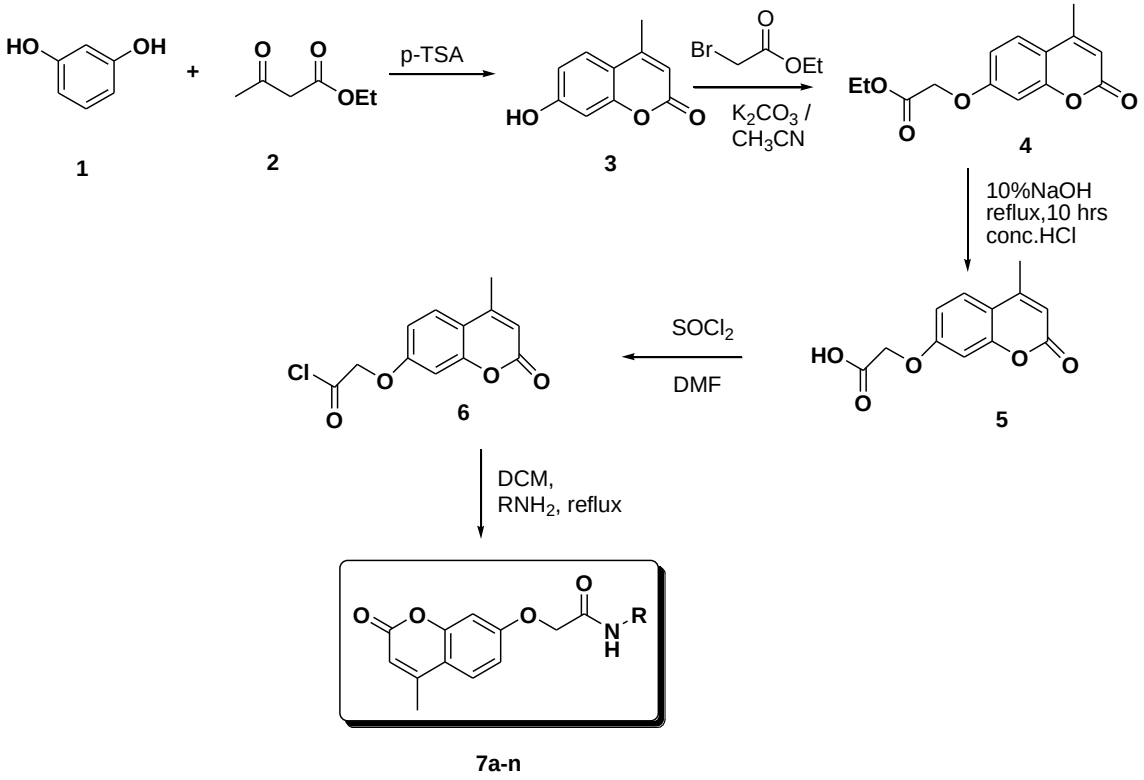
***Section-A*:**

In recent years, multiple drug resistance has been developed due to indiscriminate use of existing antimicrobial drugs in the treatment of infectious diseases and has become a global public health problem. Topoisomerases are important enzymes for DNA synthesis. Drugs that target topoisomerases have become important for both microbial and cancer therapy. The antibacterial properties of coumarins were first recognized in 1945 when Goth et al. conducted an investigation with dicoumarol and it was found to inhibit the growth of several strains of bacteria. Smyth et al reported that antimicrobial activity of 43 natural and synthetic coumarins on clinical isolates of methicillin resistant *Staphylococcus aureus* (MRSA) strains and also demonstrated their resistance modifying activity (RMA). A few antibiotics with the coumarin skeleton as part of their structure have been isolated. The most active of them is novobiocin, isolated from *Streptomyces niveus*, which is mainly active against Gram-positive bacteria. These coumarin antibiotics are potent inhibitors of DNA replication via topoisomerase II (Bacterial gyrase) inhibition.

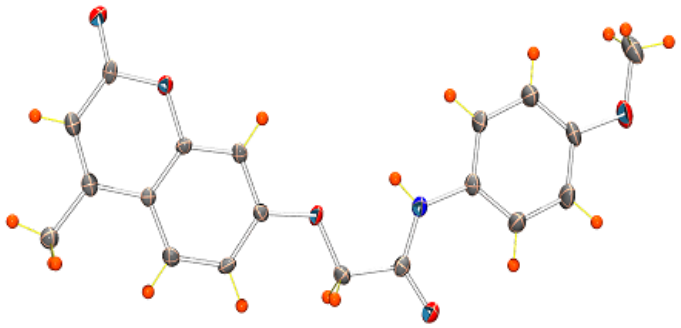
Recent reports demonstrated that 5-LOX plays a key role in progression of Cancer. Coumarin and related derivatives have been used as inhibitors of lipoxygenase (LOX) and cyclooxygenase (COX) pathways of arachidonic acid metabolism. Products of the 5-lipoxygenase pathway are thus important mediators of inflammation, cancer. Inhibitors of the 5-LOX and Histamine receptor antagonists have been used for asthma therapy.

***Section-B*:**

In the present study we described the synthesis and biological applications of coumarin derivatives. All the synthesized compounds were characterized by advanced spectroscopic data and single crystal XRD studies were performed on selected four compounds to study the polymorphism and space grouping. But the compounds didn't show polymorphism. Further, compounds are tested for the biological applications *viz)* anti-microbial activity on human pathogenic bacteria and fungi which are isolated from the infected patients and anti-cancer activity on NCIH 292 and HCC 827 lung cancer cell lines. 5-LOX study & Histamine antagonistic activity on guinea pig ileum and anti-oxidant activity were also invetigated.



1 2 3 4 5 6 7a-n



ORTEP diagram of 7j

Anti-microbial activity on Human pathogens:

Structure activity relationship (SAR) point of view, the studies reveal that aromatic carboxyl amide coumarins are potential in anti-microbial activity followed by alicyclic and aliphatic straight chain carboxyl amide coumarins. Molecular docking studies were performed and their mechanism of action predicted as similar to ciprofloxacin.

5-Lipoxygenase inhibitory activity:

The 5-LOX study on the tested compounds resulted that that compound **7b** with propyl containing carbyloxy acetamide coumarin exhibited significant inhibitory activity while N-morphylyl carbyloxy acetamide coumarin showed less 5-LOX inhibitory activity. N - (2-hydroxy) phenyl (**7l**), N-piperidyl (**7g**), iso butyl (**7d**) carbyloxy acetamide coumarins exhibited considerable 5-LOX inhibitory activity.

Histamine antagonistic activity:

Preliminary *ex vivo* histamine antagonistic activity of newly synthesized coumarinyloxy acetamide derivatives were assessed based on percent histamine induced contraction response of guinea pig ileum.

In silico and preliminary *ex vivo* studies results demonstrated potent histamine antagonistic activity of **7j** on H_1 receptors of guinea pig ileum. Results are encouraging and further investigation are under progress.

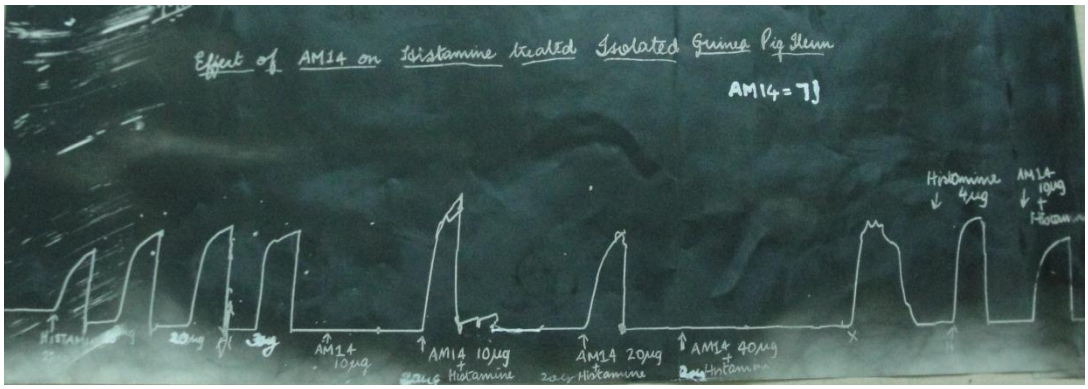


Fig-2.32: Effect of compound 7j on guinea pig ileum compared with Histamine

CHAPTER-III:

Section-A: Literature review

β-amino alcohols are the attractive intermediates for many organic compounds, particularly biologically active compounds of natural and synthetic origin. They have been widely used as β-blockers, insecticidal agents and chiral auxiliaries.

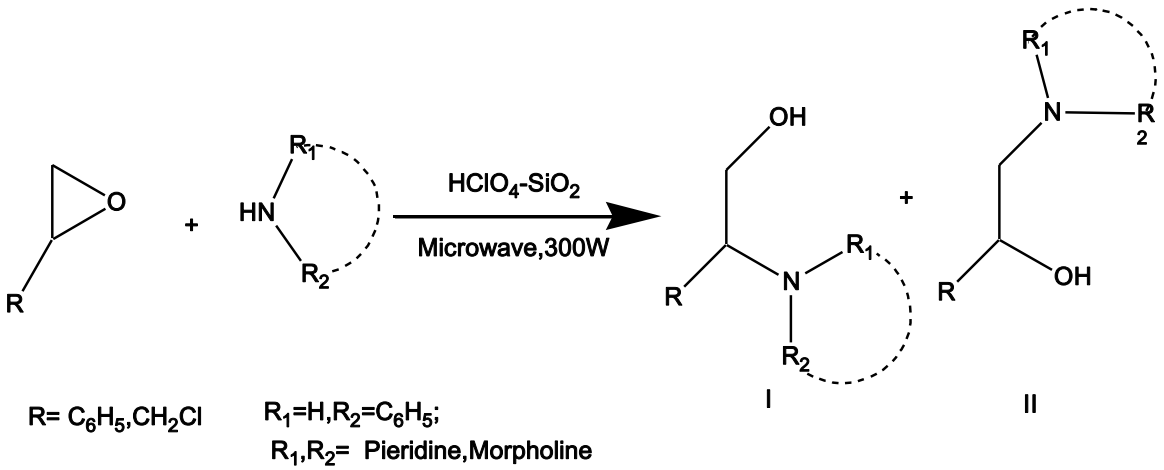
The classical approach for the synthesis of 2-amino alcohols, involving nucleophilic opening of epoxides by amines, which requires the treatment under heating and works less well with poorly nucleophilic amines, lacks appreciable regioselectivity and poses problems in dealing with sensitive epoxides due to the potential side reactions at high temperatures, and needs excess amine. Various protocols have been developed for activating epoxides rendering them to be more susceptible to nucleophilic cleavage by amine.

However, these methodologies suffer from one or more disadvantages such as long reaction times, elevated temperatures, high pressure, moderate yields and regioselectivities, use of air and moisture sensitive catalysts, use of halogenated solvents, requirement of stoichiometric amounts of catalyst, use of costly reagents/catalysts, the need to use special apparatus, rearrangement to allylic alcohols, potential hazards in handling pyrophoric/moisture sensitive reagents in the preparation of the catalyst, and in most of the cases being applicable to aromatic amines only. Therefore, the development of a better catalyst is in high demand. Besides reducing the reaction time and increasing the yield and efficiency of the process, most of them focused on a cleaner way to obtain β-amino alcohols.

***Section-B*: Present work**

A variety of β-amino alcohols were synthesized by mixing aryl amines, epoxides and catalyst and placed in a microwave oven for specific time intervals. This method is simple, requires short reaction times, high yield and the reaction proceeds under solvent-free conditions. Besides the synthesis of 2-amino alcohols a cardiovascular drug *viz*) Proapranolol was synthesized by adopting the methodology. All the synthesized compounds were characterized by advance spectral techniques.

In conculsion, $HClO_4$–SiO_2 catalyst effectively promotes the ring opening reaction of epoxides under microwave conditions. The ring opening of terminal epoxides such as styrene oxide produces secondary alcohols in good yields. The notable advantages of this procedure are: (a) reasonably good yields; (b) shorter reaction times; (c) mild reaction conditions; (e) in tune with green synthesis avoiding solvents; (f) reusability of catalyst.



CHAPTER-IV:

***Section-A*: Literature review**

Heterogeneous catalysis plays a central role in generating the feed stock for making the synthetic materials that we use every day, from fuels to fertilizers. New experimental techniques have brought fresh insights into this form of catalysis, and it now seems that there are more similarities between enzymes and heterogeneous catalysts that initially meet the eyes.

An extensive application of heterogeneous catalysis in synthetic chemistry can help to achieve new selective reactions to lower formation of waste and finally render more attractive synthetic process for both environment and economic point of view.

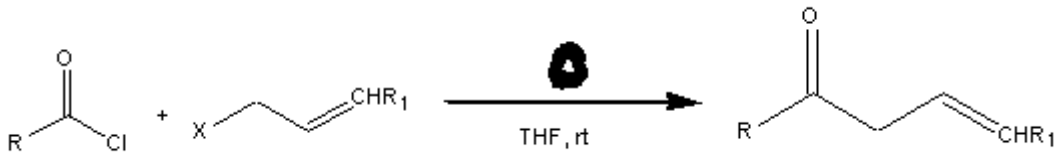
Recent reports reveal that magnetic nanoparticles are efficient catalysts and they can be easily separated from reaction mixture. The high surface area to volume ratio of metal oxide nanoparticle is mainly responsible for their catalytic performance. Copper ferrite nano material is one such reusable catalyst which shows profound catalytic activity in organic synthesis

β, γ – Unsaturated Ketones are versatile synthons in the synthesis of natural products. In general acylation of olefins produces β, γ – unsaturated ketones, but α, β– unsaturated ketones may also be generated. The synthesis is complicated by a tendency towards prototropic rearrangement producing conjugated α, β– unsaturated ketones. Hence there is a need to develop new synthetic methodologies for the convenient synthesis of β, γ – Unsaturated Ketones.

***Section-B*: Present Work**

A variety of allylketones were prepared by mixing allylhalide and acid chloride in presence of catalytic amount of copper nano ferrite in stoichiometric portions using tetrahydrofuran as solvent and stirred at room temperature. All the synthesized compounds were characterized by advance spectral techniques.

In conclusion, we report here for the first time an efficient protocol in the synthesis of β, γ-unsaturated ketones using copper ferrite nano material. The notable advantages are inexpensive, heterogeneous reusable catalyst; mild reaction conditions, high yields of products, shorter reaction times, no isomerization during the reaction and easy workup.



1a-j
2a-d

3a-j
4a-d

R= Alkyl, Aryl R_1= H, C_6H_5 X= Br, Cl

● = Copper ferrite nano particle

CHAPTER-V:

Section-A: Survey of Literature

Currently, metal nanoparticles such as gold and silver have drawn immense attention due to their potential applications as catalyst, optoelectronic nanodevices, substrate for surface-enhanced Raman spectroscopy (SERS), chemical and biological sensors and biomedicine materials. Concerning the synthesis of metal nanoparticles, especially silver nanoparticles, numerous methods such as chemical reduction, thermal reduction, electrochemical reduction, and other reductions by microwave, ultrasonic, γ-ray irradiation, UV irradiation and templates, have been reported in the literatures. Among them, the most common approach is chemical reduction using sodiumborohydride and citrate as the reductant and protection agent respectively to fabricate silver nanoparticles. The size and shape of Ag nanoparticles are extremely important due to their effects on the physical and chemical properties. A variety of Ag nanoparticles with different shapes such as nanoprisms, nanorods, nanowires and nanocubes have been successfully prepared to explore the shape dependant optical and electronic properties.

Section-B: Present Work

In the present work, we report the formation, morphology and study of "ac-impedance" of the Thio semi carbazide-capped silver and gold nanoparticles. This method utilizes a simple chemical reaction of metal iodide and sodiumborohydride. The advantage of this method is ease of preparation, convenience in use and especially, the obtained nanoparticles are uniform in their shapes and sizes. Time-dependent UV-Vis spectroscopy and Scanning electron microscopy (SEM) are employed to monitor the silver formation process of the nanoparticles. Specifically, we observed changes in the shapes of the

nanoparticles (during the formation of the nanoparticles). This may be helpful in understanding the growth of the nanoparticles and creates a new dimension in controlling the shapes of the nanoparticles.